Author's response to reviews

Title: GoLBeT [Gojjam Lymphoedema Best practice Trial]: description of study protocol for a randomised controlled trial of effectiveness of treatment for podoconiosis (non-filarial elephantiasis).

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Author's response to reviews: see over
Dear Editors-in-Chief,

We are pleased to resubmit for publication on Trials the revised version of MS: 1984637592148982, “GoLBeT [Gojjam Lymphoedema Best practice Trial]: description of study protocol for a randomised controlled trial of effectiveness of treatment for podoconiosis (non-filarial elephantiasis)”. We appreciate the comments made by the reviewer (Date: 9 April 2015). We have gone through each carefully and noted responses below, with references to the locations in the manuscript that the changes are to be found. The reviewer’s comments and editorial requests are in normal font and our responses are in bulleted form, in blue.

Reviewer’s Comments:

1) Table 1 and Endpoints and Outcomes and measurements: Is it possible for you to describe in more detail, how you plan to assess the number of acute attacks, especially in patients who are not able to write and therefore will have difficulties to write their own diary?
   • Yes, this was a real concern of the trial steering committee and thoroughly deliberated by the trial team.
   • We have added the following statement under outcomes and measurement on p12: ‘Considering most of the patients are unable to write, the trial team have designed the diary in such a way to put a check mark (□) or a dash (-) under the boxes corresponding to drawings; showing a healthy patient (working in the field) and a patient experiencing acute attacks (shown in bed) for each day of the month. During the pilot phase, patients had minimal difficulty in marking the diaries based on their experiences of acute attacks. For the trial, patients will be trained on how to complete at the outset and those who may have difficulty (including the elderly or visually impaired) will be requested to have their diaries filled by family members or neighbors who are able to read and write. In addition, diaries of patients in the immediate treatment group will be checked and collected at every monthly intervention meetings, while all diaries of patients in the control group will be checked on the first month and a random 10% on subsequent months.’

2) Table 1: Regarding the clinical stage of disease you mention a scale specifically developed for use in podoconiosis patients. Could you please add a reference or describe the staging in more detail?
   • The clinical stage of the disease was specifically developed for podoconiosis patients by Tekola et al in 2008. We have inserted the reference in Table 1 and on page 20 (reference number 22).

3) Table 1: Who developed the scale to measure the perceived stigma? Could you please add a reference?
   • The scale was developed, tested and standardized to measure stigma related to podoconiosis by Franklin et al 2013. We’ve included the reference in Table 1 and on page 20 (reference number 24).
• We have also added a reference for the Quality of Life measure using a validated Amharic translation of Dermatology Life Quality Index. The reference is included in Table 1 and on page 20 (reference number 23).

4) Sample size and statistical methods: Could you please describe how you calculated the 40% increase to enable adjustment for 4 confounders? What will be the statistical method to analyse your primary outcome? This should be stated in the statistical methods.

• We used the suggestion from Kirkwood and Sterne (reference number 16) who cite Smith and Day Int J Epidemiology 1984, 13; 356-65 who state that 10% is an upper bound of an inflation factor per confounder.

• We have added a sentence into the manuscript saying how the primary analysis will be a test of mean ADLA events per arm.

5) Randomisation: it is not clear how you plan to do the randomisation, are you going to randomize per kebele or per patient. If you randomise per patient, how do you plan to avoid a bias resulting from the fact that a participant for example, who is in the immediate treatment group shows his neighbor, who is in the delayed treatment group, what soap or ointment to use and how to apply the hygiene interventions? It is also not clear, why you do not randomise after checking the eligibility criteria as you state it in your study timeline (table 3). Table 3 and the text are contradictory.

• The trial is individually randomised and outcomes are measured at individual level. Using kebeles as the randomisation unit (i.e. conducting a cluster-randomised trial) would greatly decrease the power of the study to find an effect – depending on the inter- and intra-kebele variance, it would be necessary to randomise something in the order of 50 kebeles.

• The concerns are effectively all about the same issue – contamination – which was one of the greatest concerns of the Trial Steering Committee, and one that they specifically investigated in a site visit in April 2013. Staff of the IOCC Podoconiosis Project in the study site told the study team that despite explaining that treatment for podoconiosis was available through public meetings since 2010, they still had a waiting list of more than 12,000 patients. These patients live in the same gotts (villages) as patients receiving treatment, but had not bought their own soap, bandages, shoes or socks. There were several examples of patients living in the same household who did not adopt hygiene practice or share consumables. The team met a husband and wife; the husband had been receiving treatment for 3 months, but during this time the wife had not attempted self-treatment, and had waited until she was called for treatment. This is clearly disappointing in terms of the potential to mobilise the community in future, but means that contamination within the trial is unlikely. In order to minimise the effects of any contamination during the trial, if more than one eligible patient is found in a household, only one patient will be randomly selected using a lottery method which involves folded papers, the number being that of patients in the household, and only one being marked with a cross. In addition, data will be collected on potential contamination during follow-up visits.

• We agree the text is not clear. The procedure that will be followed is as described in the timeline. We have added the following paragraph to clarify the process on p8.... All patients identified by Health Extension Workers (HEWs) will be visited at home by a data collector and consent requested for preliminary evaluation against the inclusion and exclusion criteria. The
data collector will record potential willingness to take part in the trial, Geographic Information System (GIS) coordinates of the house and local contact information (e.g. kebele office, nearest mobile phone owner). Patients who appear to be eligible will then be given an appointment date for enrolment at the nearest health facility. At enrolment, all patients will be asked for full consent for the trial; be evaluated against inclusion and exclusion criteria once more, and ICT tests and baseline measurements will be carried out. Community Podoconiosis Assistants (CPAs), Data Collectors (DCs) and data supervisors assisted by the study coordinator and data manager, will enrol patients.

6) Blinding and statistical methods: In the Blinding paragraph you write that you will define an a priori analytical plan to avoid bias. That sounds as if you would develop the plan before starting with the study. But reading the statistical methods part it becomes clear that you want to develop the plan before starting the analysis. Please state it more precisely.

- Again, we agree this is not clear. To clarify we have added under the section on blinding on p9....‘the analytical plan will be developed while the intervention is in progress’, and removed the statement ‘before the analysis begins’ on p14 under ‘Statistical Methods’.

7) Adverse event monitoring: It would be more understandable for the reader if you write that you decided not to include a DSMB and then start with your arguments. This fact was not clear until one of the last sentences of the paragraph. Also in this paragraph you write that the control arm is standard of care, or no intervention. What do you mean with standard of care?

- We agree, and have changed the order of the paragraph to that effect, under ‘Adverse Events Monitoring’ (on p13).
- On p13 we have also amended the statement ‘the control arm is standard of care, or no intervention’ to read ‘The standard of comparison or the control arm is delayed intervention’.

8) Minor Essential Revisions: Last paragraph of outcomes and measurements: the sentence structure is not clear.

- We have amended the statement to read...‘all secondary outcomes will be measured following internationally validated scales where possible. Where no internationally validated scale is available, previously reported questionnaires will be used (Table 1).

9) In table 2, exclusion criteria 3, a bracket is missing, and exclusion criteria 4, the semicolon has to be deleted.

- We have now added the missing bracket on exclusion criteria 3 and removed the semicolon on exclusion criteria 4.

Editorial requests:

1) Please include a more formal statement of informed consent. Please include the statement in your Methods section explaining that you obtained informed consent from each participant.

- We’ve added a statement on page 7...“Written informed consent will be obtained from each participant”.
2) Please make sure that all authors meet the 1st point in our authorship requirement list: "all authors should have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data." Please make sure this is made clear in the Authors’ Contributions section.

- We hope this is now clear in the Authors’ Contributions section.

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